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Review Article

Advances in Chemical Composition and Biological Activity of Mexican Propolis

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Abstract

Propolis is a product created by honeybees from vegetal sources. Nowadays it is considered a medicinally or functional food because of the phytochemicals contained in it. Numerous papers have been published reporting the chemical composition of different countries around the globe due to its highly variability(phenolic compounds, sugars, terpenoids). Due to the variability in its chemical composition, various biological activities have been reported, among them are anti-inflammatory, antimicrobial, anticarcinogenic, among other. In Mexico has history on beekeeping that was modified by the Spanish conquest but endures to these days. Therefore, it is important to exploit the characteristics of the propolis of our region in order to know both their composition and beneficial properties.

Keywords: Propolis; Honeybees; Flavonoids

Introduction

Propolis is resinous material produced by honeybees, which collect secretions from plants organs and then they are mixed with beeswax and salivary enzymes [1]. Propolis color may vary from light yellow to dark brown [2]. Bees produce propolis to fill cracks in the hive, to regulate the temperature and embalm invaders [3]. The general composition comprises resins (50%), waxes (30%), essential oils (10%) pollen (5%) and other organic compounds (5%) [4]. Some compounds reported in the resin are phenolics, esters, flavonoids, aldehydes and alcohols. This natural product has attracted the attention of researchers because of its biological activity and the diversity of its composition. Since 1970's, scientists around the world have reported the chemical composition and biological composition of propolis from different countries such as Czeck Republic, Bulgaria, Croatia, Portugal, China, Netherlands, Italy, France and Brazil, among others. However, in Mexico little has been explored of the propolis of this region despite that apiculture has been an ancient activity. Pre-Colombian cultures raised stingless bees for food, medicinal and religious purposes. In the tropical region of Mexico, Mayans bred honeybees such as *Melipona beechii, Melipona domestica, Melipona fulvipes* and *Trigona sp*, in order to collect honey and wax [5]. Spanish conquerors brought with them the European bee, *Apis mellifera*, who partially replaced the native Mexican bees in recollection of bee products. Nowadays, *Apis mellifera* is the main honeybee exploited in Mexico for honey, beeswax, pollen, royal jelly and propolis. Propolis is considered only a side product derived from the hive, therefore there is no reliable source to measure the production of Mexican propolis [6]. However, it is known that the Peninsula of Yucatan has been the most productive from 2000 to 2012, in terms of honey production [7]. Propolis is commercialized in Mexico in regional markets and local producers in its raw form, but mainly it is combined with honey to make hard candies or hydroalcoholic solutions (Figure 1). The quality of propolis or propolis products is dictated by Mexican regulation NOM-003-SAG/GAN-2017 "Propóleos, producción y especificaciones para su procesamiento". This normative comprises a qualitative test of flavonoids and phenolics, oxidation index, quantification of phenolics, quantification of flavonoids, antioxidant activity (DPPH bleaching assay) and antimicrobial activity on three bacteria. It is worthy to mention that before the NOM-003-SAG/GAN-2017, there was no regulation to ensure the quality of propolis.

Chemical Composition

Research on propolis has revealed over 500 constituents: phenolic compounds, fatty acids, sugars, minerals and terpenoids [8-11]. It is known that propolis composition varies greatly depending on the geographical origin, the botanical source, the time and method of harvest and solvent used in extraction [12-13]. The Ministry of Agriculture and Rural Development has divided Mexico into five beekeeping areas, in accordance to the honey production and geographical distribution: Altiplano, Pacific Coast, Gulf, North and Peninsula of Yucatan [14]. We can assume that propolis composition would have a pattern for each region as honey does. To date, there are reports of composition from the North (A, B, C, D, E, F and G), Altipano (H), Gulf (I), Pacific Coast (J), and Peninsula of Yucatan (K, L, M and N) (Figure 2).

Figure 1: Honeybee products traded in a local market in Milpa Alta, Mexico City. Photo by Mielin: https://www.facebook.com/mielin803/photos/a.834946096589119/834946309922431/?type=3&theater.

Figure 2: Sites of collection of propolis from provinces of Mexico.
A, Caborca, Sonora; B, Ures, Sonora; C, Pueblo de Alamos, Sonora; D, Aquiles Serdan, Chihuahua; E, Parral, Chihuahua; F, Gomez Palacio, Durango; G, Fresnillo, Zacatecas; H, Silao, Guanajuato; I, Coatepec, Veracruz; J, San Cristobal de las Casas, Chiapas; K, Champoton, Campeche; L, Hunucma, Yucatan; M, Mani, Yucatan; N, Solaridad, Quintana Roo.

Phenolics and Phenolic Esters

Phenolics are natural constituents of plants that are characterized by the presence of hydroxy substituents in their structures. Together with total flavonoid content, phenolics content in propolis is another quality characteristic in Mexican regulation NOM-003-SAG/GAN-2017, which minimum content must be 5%w/w. Only samples from Caborca, Ures, Pueblo de Alamos, Aquiles Serdan, Parral, Gomez Palacio, Fresnillo, Silao and Solidaridad were studied for phenolic content, from which the Solidaridad sample did not fulfilled the Mexican regulation. Sample from Solidaridad showed no content of phenolics since the major compounds were terpenoids. Argentinean and French propolis possess similar phenolic content [15-16].

Flavonoids

Table 1: Flavonoids and phenolics isolated from *Sonora propolis* and tested for antiproliferative activity.

	Compound
1	Chrysin
2	(7′′R)-8-[1-(4′-hydroxy-3′-methoxyphenyl) prop-2-en-1-yl] chrysin
5	4′,5,7-trihydroxy-3,3′- dimethoxyflavone
7	Apigenin
13	Pinocembrin
14	(2R,3R)-3,5-dihydroxy-7-methoxyflavanone 3-(2-methyl) butyrate
22	(2R,3S)-8-[4-phenylprop-2-en-1-one]-4′,7-dihydroxy-3′,5-dimethoxyflavan-3-ol
23	Galangin
31	(7′′R)-8-[1-(4′-hydroxy-3′-methoxyphenyl) prop-2-en-1-yl] galangin
36	Alpinone
37	(2R,3R)-alpinone-3-acetate
40	Pinobanksin-3-O-acetate
43	Pinobanksin-3-O-propanoate
47	Pinobanksin-3-O-isobutyrate
63	Benzyl (E)-3,4-dimethoxycinnamate
65	3,3-dimethylallyl (E)-ferulate
66	Isopent-3-enyl (E)-ferulate
67	Benzyl (E)-ferulate
68	(E)-cinnamyl (E)- isoferulate
72	Benzyl (E)-p-coumarate
75	(E)-ferulic acid
76	(E)-cinnamyl (E)-p-coumarate
81	2-acetyl-1,3-di-(E)-feruloylglycerol
82	(E)-p-coumaric acid

Flavonoids are the most reported compounds in propolis around the world. The content of flavonoids is considered to reflect the quality of the propolis, as the Mexican regulation NOM-003-SAG/GAN-2017 stablishes the requirement of minimum of 0.5%w/w of flavonoids. However, only samples collected in the regions Aquiles Serdan, Parral, Gomez Palacio, Fresnillo and Silao were assessed for this parameter and found to fulfill the content of flavonoids. Table 1 depicts the types of flavonoids isolated from the propolis samples. Pinocembrin was the most reported compound in Mexican propolis, in ten out of fourteen samples, followed by Chrysin in six out of fourteen samples. Both flavonoids, together with galangin, kaempferol, rhamnetin and epoxypinocembrin chalcone, have been identified in poplar bud exudates [17]. In fact, pinocembrin is considered the marker of poplar propolis [18], therefore it is found in propolis from Spain, France, China, Portugal, Rumania, Croatia, Turkey, New Zealand, Poland, Argentina [12,19-27].

Pterocarpans

The major components of South American red propolis (eg. Cuba and Brazil) are isoflavans, isoflavons and pterocarpans [28]. The sample of the region Champoton turned to be the only one containing pterocarpans and isoflavonoids, hence it could be excluded from the classification of poplar type and considered as red propolis.

Triterpenoids

Triterpenoids are natural occurring compounds in plants, which have anti-inflammatory, hepatoprotective, analgesic, immunomodulatory, antimicrobial, antimycotic, virostatic, and tonic effects [29]. Hunucma and Solidaridad samples contained exclusively triterpenes, this fact excludes them from the poplar type, red type or any other, since there is no type of propolis defined solely on triterpenes. However, the high content of triterpenes has been found in propolis from Ethiopia, being α- and β-amyrins and amyryl acetates the major compounds [30]. It is also similar to geopropolis from Mani (See Section Geopropolis). Botanical origin Depending on the ecosystem, honeybees will collect resins from different source plants, choosing appropriate representatives of the local flora [31].

Salatino and coworkers [18] made a classification of propolis, according to its geographic zone, chemical composition and botanical source reported in literature, into five types: I, from Populus section Aigeiros; II, from Baccharis dracunculifolia; III, from Clusia; IV, from Macaranga and V, Cupressaceae. According to this classification, Mexican propolis belongs to type I propolis, the temperate poplar propolis. Bees seem to gather the resins from Populus species and their hybrids. As for the tropical regions, the plant sources are rich of prenylated benzophenones, diterpenes and flavonoids [4]. As mentioned before, Mexican propolis falls into the classification of poplar type or type I. However, this is true for samples North, Pacific Coast and Gulf, since Pinocembrin and other flavonoids and phenolics were found as major constituents. The most common source from these compounds is the Populus genus, in fact the composition of Populus bud exudates have been studied to corroborate the botanical origin [17]. In Mexico is not well reported the species and abundance of Populus present throughout the country. Nevertheless, it is known that flavonoids such as pinocembrin, pinobanksin 3-acetate, tectochrysin, galangin, and chrysin have been found in *Populus nigra* [28]. Secondary sources visited by Apis mellifera are birch, alder, oak, pine and hazel. The southeast region of Mexico has tropical weather which is directly reflected on the chemical composition of propolis. Champoton, Hunucma, Mani and Solidaridad samples have a different composition from the rest of the country (See Section Chemical Composition), since these regions are considered to have a tropical weather. In tropical or subtropical areas, poplar trees are scarce, as a result, bees visit another type of trees. Two potential sources used by the bees for their production of propolis in Yucatan and Quintana Roo are *Bursera simaruba* and *Lysiloma latisiliquum* [20,32]. Dalbergia is another probable source of resin material in this region, because some compounds isolated from these samples (eg. (-)-Mucronulatol, (+)-Vestitol and (-)-Melilotocarpan A) are related to Dalbergia exudates and Caribbean and Brazilian propolis.

Biological Activity

Poplar type propolis is characterized by flavonoids, phenolic acids and their esters as bioactive constituents [28]. Particularly, flavonoids are associated to a broad spectrum of health effects because if their antioxidant, anti-inflammatory, anti-mutagenic, antimicrobial, anticarcinogenic and vascular activities [33].

Anticancer

Silao extract showed an inhibition of proliferation of rat C6 glioma cell line comparable to temozolamide, on the other hand, it did not efficiently inhibit human cervical cancer cell lines (HeLa, SiHa, and CaSki) proliferation compared to cisplatin [34]. Alday and coworkers [35] tested the antiproliferative activity of the methanolic extract of Sonora and the flavonoids isolated from it, on B cell lymphoma cell line M12.C3.F6. The methanolic extract exhibited an inhibitory concentration (IC_{50}) of 20.6±0.5μg/mL, while the IC_{50} of the flavonoids pinobanksin-3-O-propanoate, pinobanksin-3-O-butyrate, pinobanksin-3-O-pentanoate, pinobanksin, CAPE, galangin, chrysin ranged from 17.3μM to 76.6μM. Moreover, the extract showed to induce apoptosis through loss of mitochondrial membrane potential and activation of caspase 3, 8 and 9. Flavonoids and phenolics listed in Table 1 were isolated. These compounds were evaluated for the preferential cytotoxicity on PANC-1 human pancreatic cancer cells, cytotoxicity was expressed as PC_{50} [36]. The PC_{50} ranged from 4.6 to 98.9μM, showing a great potential for antiproliferative activity.

Hernandez and coworkers [37] tested the antiproliferative effect of Caborca, Ures and Pueblo de Alamos samples on human lung carcinoma A-549, human colonic adenocarcinoma LS 180, human cervix carcinoma HeLa , normal subcutaneous connective tissue NCTC clone L 929, murine B-cell lymphoma M12.C3.F6 and macrophage, Abelson murine leukemia virus transformed RAW. The components of propolis chrysin, xanthomicrol, acacetin, pinocembrin, naringenin, hesperetin, rutin, pinobanksin-3-acetate and CAPE, were tested as well. Pueblo de Alamos extract showed the best antiproliferative activity in all the cell lines tested in a range of 0.8 to 53.6 (μg/mL). Only CAPE, galangin, chrysin and xanthomicrol showed antiproliferative activity on most of the line cells (IC_{50} 3.2-95.4 μM), mainly on L-929, M12.C3.F6, RAW and, HeLa. These flavonoids could be partially responsible for the antiproliferative activity of propolis extracts. Flavonoids can exert anticancer effect through various mechanisms such as inactivation of oxygen radicals (antioxidative), binding to electrophiles, induction of phase 2 detoxification enzymes, increase in apoptosis, inhibition of cell proliferation and inhibition of lipid peroxidation [38].

Anti-Inflammatory

Chiapas (J) extract showed anti-inflammatory activity comparable to indomethacin (IC_{50} 1.21 and 0.84 mg/ear, respectively) in the model of ear edema in mice by 12-O-tetra-decanoylphorbol-13-acetate. Besides diminishing histologic signs of inflammation, J decreased the activity of myeloperoxidase [39]. The flavonoids pinostrobin, izalpinin, cinnamic acid, kaempferol, 3,3-dimethylallyl caffeate, isopent-3-enyl caffeate, 3,4-dimethoxycinnamic acid and rhamnetin did not show anti-inflammatory activity. Whereas pinocembrin had comparable effect to celecoxib (IC_{50} 2.53μmol/ear and IC_{50} 0.91μmol/ear, respectively) and to indomethacin (91.09±3.66% inhibition and 91.09.09±0.006%, respectively). The authors attribute to pinocembrin the anti-inflammatory effect observed in the propolis extract because of its high myeloperoxidase inhibition. Research on pinocembrin has revealed that it downregulates TNF-α, IL-1β, and IL-6, also suppresses IκBα, JNK and, p38MAPK [40]; which are some mechanisms that additionally explain the anti-inflammatory effect.

Antidiabetic

Chihuahua (D) propolis extract administered to streptozotocin induced diabetic mice reduces blood glucose levels and increases serum insulin levels. The pancreatic islets were found to contain insulin in contrast to the diabetic controls. There was found that the activity of antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase were restored in the treated mice in compare to non-treated mice [41]. The observed hypoglycemic activity could be the result of the secretagogue and antioxidant effects of the extract. Pinocembrin has a potential therapeutic use in diabetic nephropathy, a chronic complication of diabetes mellitus. When pinocembrin was administered to streptozotocin-induced hyperglycemic rats, before diabetic nephropathy establishment, it was able to improve survival and, to partially decrease blood glucose, lipids and renal function. These results correlated with a decrease in oxidative stress. However, when pinocembrin was administered once renal structural damage was stablished, pinocembrin improved triglycerides and LDL, but it worsens all renal function parameters due to increases ROS [42].

Iranian propolis has similar effects to Mexican propolis, on streptozotocin-induced hyperglycemic rats. The ethanolic extract of Iranian propolis avoided body weight loss and, high FBG and MDA content, as well as reducing GBM thickness and glomerular area. These results indicate that propolis protection was due to its antioxidants properties [43]. Various flavonoids have been studied for its antidiabetic properties. Naringenin has showed to inhibit of intestinal α-glucosidase, to improve insulin sensitivity and glucose tolerance [44-45]. On the other hand, chrysin inhibits TNF-α pathway and downregulates the expression of TGF-β, fibronectin and collagen-IV proteins [46]. These flavonoids, reported to be present in Mexican propolis, with their aforementioned mechanisms and their known antioxidative activity, could explain the antidiabetic effect described for the Chihuahua propolis.

Antimicrobial

Ethanolic extract of Silao (H) propolis and, the isolated flavonoids and phenolic acids were tested against oral pathogens *Streptococcus mutans, Streptococcus oralis, Streptococcus sanguinis,* and *Phorphyromonas gingivalis*. The inhibitory effect on the microorganisms ranged between 125-500μg/mL for the propolis extract and 128-1024μg/mL for the isolated compounds. Chiapas propolis (J) showed moderate inhibitory effect (MIC=250μg/mL) on *Mycobacterium tuberculosis* H37Rv in the Resazurin Microtiter Assay [39]. Sonoran propolis (Caborca, Ures and Pueblo de Alamos) samples were investigated for the effect on clinical isolates of *Staphylococcus aureus*. Ures sample had the highest inhibitory activity (MIC 200μg/mL) while Pueblo de Alamos showed no activity [47]. These samples also inhibited the growth of various Vibrio species such as cholerae (serotypes Inaba, non-O1, Ogawa), *vulnificus*, *alginolyticus*, *fluvialis* and parahemolyticus, in a range of 50-200μg/mL. Furthermore, propolis constituents were tested against *V. cholerae*, showing high (galangin and CAPE), moderate (pinocembrin, hesperetin and naringenin) and low (chrysin and acacetin) activity [48].

Quintero-Mora and coworkers [49] investigated the inhibitory activity on *Candida albicans* of various propolis from State of Mexico, Veracruz and Puebla not shown in Figure 2, fresh prepared and commercial extracts. The MIC was highly variable and ranged from 0.6 to >10 mg/mL. Recently Al-Ani et al. [50] tested propolis collected in Germany, Ireland and Czech Republic on Gram-positive (*Staphylococcus aureus, Staphylococcus saprophyticus, Staphylococcus epidermidis*, MRSA/NCTC, VRE Van B, *Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus oralis, Streptococcus agalactia, Streptococcus thermophilus, Bacillus subtilis, Enterococcus casseliflavus*), Gram-negative bacteria (*Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, Escherichia coli* O157:H7, *Pseudomonas aeruginosa, Salmonella choleraesuis, Shigella flexneri, Haemophilus influenzae, Acinetobacter baumannii, Burkholderia cepacia, Enterobacter clacae, Yersinia enterocolitis*) and fungi (*Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida krusei*). The MICs for Gram-positive bacteria ranged from 0.08mg/mL to 5mg/mL; 0.6mg/mL to 5mg/mL for Gram-negative and, 0.1mg/mL-5mg/mL for fungi. Thus, the European propolis showed higher inhibitory effect than that observed in Mexican propolis. Antimicrobial activity of propolis is attributed to the phenolic content and particularly, to the flavonoids galangin and pinocembrin [51]. The reported mechanisms are membrane damage, inhibition of acid nucleic synthesis, and inhibition of energy metabolism [52].

Antiparasitic

Sonoran propolis (Caborca, Ures and Pueblo de Alamos) samples were investigated for the effect on Giardia lamblia trophozoites. Ures sample showed the highest activity (IC_{50}=63.8μg/mL), Pueblo de Alamos had low activity (IC_{50}=222μg/mL) and Caborca did not show significant inhibition on the trophozoite growth. In the microscopic analysis of the trophozoites, there were morphological changes on the trophozoites treated with B compared to the control trophozoites, as well as cellular debris. The six main constituents of Sonoran propolis (CAPE, naringenin, hesperetin, pinocembrin, chrysin and, rutin) were tested on *G. lamblia* trophozoites, being CAPE the most active (IC_{50} 63.1±0.9 μg/mL) and, hesperetin (IC_{50} 149.6±24.8μg/mL) and pinocembrin (IC_{50} 174.4±26.9μg/mL) the weakest ones [53]. European propolis extracts collected in different regions of the United Kingdom, Bulgaria and Lithuania, showed activity against human and bee parasites. The extracts decreased the survival of wild-type and resistant strains of Leishmania mexicana with a EC_{50} 0.1-5.67μg/mL and 0.29-1.55μg/mL, respectively; wild-type and resistant strains of *Trypanosoma bruce*i with a EC_{50} 3.67-18.4μg/mL and 2.5-25.0μg/mL, respectively; *Trypanosoma congolense* with a EC_{50} 1.96-35.7μg/mL and, *Crithidia fasciculata* with a EC_{50} 2.58-23.8 μg/mL. Orthogonal partial least squares analysis of the propolis activity and the LC-MS profile, revealed that butyrate ester of pinobanksin is related to the high activity against *Trypanosoma brucei*, methyl esters of chrysin are related to high activity against *Trypanosoma congolense*, methyl esters of galangin and pinobanksin are related against *Crithidia fasciculata*, but no compounds were found to be related to the anti-Leishmanial activity [54]. The activity of Mexican propolis and European propolis may not be comparable since they inhibit different parasites, however, they both bring out the potential of temperate propolis and flavonoids against parasites.

Geopropolis

Stingless bees mix resinous material from plants, bees wax and soil to form geopropolis. This type of bees, also called Meliponinos, is present in all tropical zones over the world and around 400 to 500 species are known [55]. In Mexico 46 species have been identified, being Plebeia, Trigona, Melipona and Trigonisca the most diverse genera [56]. Stingless beekeeping was present in the cosmogony and mythology of Mesoamerican civilizations, as well as a source of staple food [57]. The most exploited species of Meliponinos, for their honey and wax, are *Melipona beecheii* in the Mayan area and *Scaptotrigona mexicana* in the Nahua area [56]. Despite the important historical background of stingless bees in Mexico, there is scant research on the propolis made by Meliponinos native to this country. The available research on geopropolis is from Brazil yet is not as abundant as the propolis research. Geopropolis differs from propolis because of the mineral and soil content, and the absence of plant trichomes of the former, despite of this, geopropolis has similar functions in the hive [58]. Biological activities reported for geopropolis are gastroprotective, antimicrobial, antioxidant, anticancer, anti-inflammatory, sedative, antimutagenic [59-63].

Regarding the chemical composition, polyphenols, phenolic acids, flavonoids, hydrolysable tannins, triterpenoids and, saponins [60,64-65]. Pentacyclic triterpenes were the main compounds identified in *Melipona beecheii* geopropolis from Mani (L), for instance lupenone, α-amyrin and β-amyrin [66]. Volatile compounds comprise approximately 10% of the propolis constituents and they confer odor and pharmacological effects. Pino et al. [67] compared the volatile fraction of propolis from *Apis mellifera* and *Melipona beecheii* from Yucatan, they were able to establish characteristic compounds of each type of propolis. Honeybees propolis' exclusive volatiles were styrene, phenylacetaldehyde, trans-sabinene hydrate, nonanal, decanal, 2-undecanone, cyperene, cis-α-bergamotene, massoia lactone, ar-curcumene, cis-calamenene, cadina-1,4-diene, α-cadinene, β-eudesmol, α-bisabolol, neryl linalool, geranyl linalool, manoyl oxide, kaur-16-ene, pentacosane and heptacosane. Stingless bees geopropolis' exclusive volatiles were santolinatriene, 6-methyl-5-hepten-2-one, α-phellandrene, δ-3-carene, p-menth-1-ene, p-cymenene, α-pinene oxide, chrysanthenone, trans-p-mentha-2,8-dien-1-ol, cis-limonene oxide, verbenyl ethyl ether, germacrene A, α-dehydro-ar-himachalene, β-vetivenene and humulene epoxide I. However, both samples had in common the compounds α-pinene, β-pinene, trans-verbenol, α-copaene, β-bourbonene, β-caryophyllene, spathulenol and caryophyllene oxide. Geopropolis from Coatepec, Veracruz was subjected to HS-SPME-GC-TOF-MS analysis to identify volatile components. The major compounds identified in the total current ion were β-fenchene, styrene, benzaldehyde, (Z)-ocimenone, α-pinene, m-cymene, trans-isocarveol, limonene and β-pinene [68].

Conclusion

The chemical composition of Mexican propolis from Altiplano, Pacific Coast, Gulf and North zones is like to that reported from other temperate zones of the world. Meanwhile, the Peninsula of Yucatan zone differs to the rest of the country because of its tropical weather and flora. The most exploited species of honeybee in Mexico is the *Apis mellifera*, nevertheless the native honeybees are also cultured. Biological activity reported to date is anticancer, anti-inflammatory, antidiabetic, antimicrobial and antiparasitic, which are the activities already documented for temperate propolis. Further research is needed on propolis from other states of the country, in order to accurately characterize and classify it, as well as the study of the geopropolis made by Meliponinos. Finally, all samples studied must be subjected to the criteria established in the Mexican regulation NOM-003-SAG/GAN-2017, for the purpose of making reliable comparisons.

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